CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicant respectfully requests that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

REMARKS

Applicant respectfully requests reconsideration and allowance of this application in view of the amendments above and the following comments.

The only amendment to the previous claims is that claim 8 has been made dependent on claim 13.

Claims 8-12 and 15 were withdrawn from further consideration as being drawn to a nonelected invention. In response, Applicant points out that claim 8 has been made dependent on claim 13. Since claims 9-12 depend directly or indirectly from claim 8, these claims also

depend indirectly from claim 13. As a result, claims 8-12 are subject to the current rejoinder practice, and, therefore, should be rejoined and considered in the event that claim 13 is found to be allowable. An early notice that the Examiner will follow this procedure is earnestly solicited. In the event that the Examiner will not follow this procedure, then Applicant respectfully requests an explanation why the rejoinder practice is not applicable here.

Claims 13 and 14 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicant points out that the only prior art rejection is the rejection of claim 13 over the Ohkuma reference, which prior art rejection, as discussed below, is easily overcome by perfecting Applicant's priority claim. Other than this, the Examiner cites no prior art establishing either that the invention was known or, at the time it was made, would have been obvious to persons skilled in the art. Thus, the record reflects that Applicant was the first to develop Ru(II) complex catalysts of the type presently claimed. As such, Applicant is a pioneer in a sense, and is entitled to the broad claims to the broad concept. *See, for example, In re Hogan et al.*, 194 USPQ 527, 537 (CCPA 1977):

> "The record reflects no citation of prior art disclosing a solid polymer of 4-methyl-1-pentene, which may suggest that appellants at least broke new ground in a broad sense. On remand, appellants may be found to have been in fact the first to conceive and reduce to practice "a solid polymer" as set forth in claim 13. As pioneers,

if such they be, ***they would deserve broad claims to the broad concept.***" [Emphasis added.]

The Examiner objects to the following claim language:

1) "support bonded bisphosphine ligand";

2) "diamine ligand";

3) "bisphosphine or derivative capable of polymerization"; and

4) "linking;"

and would apparently have Applicant limit the scope of the objectionable language. However, Applicant declines to limit the claims inasmuch as the claim language is believed to be clear and definite when read in the light of the instant specification.

In this regard, Applicant would remind the Examiner that when considering the question of indefiniteness claims are not to be considered in a vacuum, but in the light of the specification to which they are attached. *In re Angstadt et al.*, 190 USPQ 214, 217-218 (CCPA 1976). In this instance, Applicant submits that the instant claims would be clearly understood by persons skilled in this art given the instant specification.

Regarding the phrase "support bonded bisphosphine ligand," Applicant points out that the specification beginning on page 2, line 2, and continuing through the subsequent pages gives a detailed explanation of the invention, which is clearly broad in scope. Respectfully, the Examiner has not explained why the scope of the objectionable phrase is in any way inconsistent with the scope of the claims as the scope of the claims would be understood given the instant specification. In the absence of such inconsistency, and in view of the fact that no prior art anticipates or renders obvious the broad subject matter, Applicant submits that limitation to specific structures is unnecessary, as a matter of law.

Regarding the phrase "diamine ligand," Applicant submits that a person having ordinary skill in the art knows exactly what is or is not a diamine ligand. Moreover, examples of suitable diamines are given at page 17, lines 23-28. Again, in view of the record, Applicant perceives no need to limit the claims to particular diamine ligands.

Regarding the phrase "bisphosphine or derivative capable of polymerization," the role of polymerization is explained, for example, at page 8, lines 14 ff.

Regarding the term "linking," linking is discussed at page 6, lines 23 ff, and also on page 8, lines 6 ff. Respectfully, again, Applicant submits that what is intended is clear from the instant specification, and, therefore, the Examiner should not require a limitation.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claim 13 was rejected under 35 USC § 102(a) as being anticipated by Ohkuma, *Adv. Synth. Catal., 343:* 369-75 (April 2001). As the Examiner apparently would concede, the instant application claims priority benefits from German Patent Application No. 101 05 104, which was filed on February 5, 2001, and, therefore, predates Ohkuma. However, the Examiner points out that benefit of such priority application cannot be accorded until Applicant files a certified English language translation thereof. In response, Applicant submits the requisite certified English language translation of the priority application. Applicant further submits that in view of the certified English language translation, Ohkuma is removed as prior art. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Applicant believes that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicant also believes that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
NORRIS McLAUGHLIN & MARCUS, P.A.

By _____
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment under 37 CFR § 1.111 is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below:

Date: January 29, 2004

By: _____
Jennifer Archer

I, Ruth Christophersen, of Feldstrasse 73, D-40479 Düsseldorf, hereby declare that I am conversant in the German and English language and I am the translator of the document attached.

I hereby certify to the best of my knowledge and belief, the attached document is a true and accurate translation of the German Patent Application 101 05 104.2, filed in the name of Bayer AG, Leverkusen, Germany, and assigned to Studiengesellschaft Kohle mbH, Mülheim an der Ruhr, Germany.

November 19, 2003

Ruth Christophersen

Le A 34 933

Process for the preparation of non-chiral and optically active organic compounds containing hydroxyl groups

Organic compounds containing hydroxyl groups, including those in optically active form, are important intermediates, for example for the preparation of pharmaceutical active ingredients, crop protection agents, fragrances and liquid-crystalline substances.

EP-A 718 265 discloses a process for the preparation of non-chiral and optically active alcohols in which a carbonyl compound is reacted with hydrogen in the presence of a homogeneous catalyst, a base and an organic compound containing nitrogen. The homogeneous catalyst may, for example, be a ruthenium complex containing phosphine ligands, the base may be an alkali metal or alkaline earth metal hydroxide, and the organic compound containing nitrogen may be an amine.

A disadvantage of this process is the use of a homogeneous catalyst, which hinders work-up of the reaction mixture and the preparation of products which are not contaminated with catalysts or constituents thereof. Furthermore, the isolation of the valuable catalyst or its constituents is possible, if at all, only with high technical complexity and expenditure. Finally, it is difficult to carry out processes using homogeneous catalysts in a continuous manner.

Homogeneous catalysts are characterized by high selectivities and activities which are not generally achieved by corresponding heterogeneous catalysts.

It therefore had to be taken into consideration that in the present case as well, when transferring from homogeneous to heterogeneous catalysts, any advantages, e.g. with regard to work-up of the reaction mixture, purity of the product prepared, catalyst recovery and continuous reaction procedure, can only be realised in conjunction with serious disadvantages, e.g. with regard to selectivity and activity.

We have now found a process for the preparation of non-chiral and optically active alcohols in which a carbonyl compound is reacted with hydrogen in the presence of a catalyst, a base and

optionally a diamine, which is characterized in that the catalyst used is a support-bonded Ru(II)-phosphine-diamine-Ru complex catalyst of the formula (I).

[support]-[optional modification]-[binding group]-

-[bisphosphine $\rangle RuHal_2\langle$ diamine]

(I) Hal = Cl or Br

A short time ago (Synlett 2000, No. 5 680-682), a process for the asymmetric hydrogenation of ketones became known which is carried out using a heterogeneous catalyst component which contains BINAP structural elements incorporated in the main chain. This is an oligomeric diisocyanate adduct with the name "poly-NAP" (see Tetrahedron Letters 41 (2000), 643-646), which is significantly different from the catalysts used according to the invention which contain support-bonded bisphosphine-diamine-Ru(II) complexes. The support-bonded catalysts used according to the invention are, for example in contrast to poly-NAP, insoluble in all solvents. A significant advantage of the process according to the invention is that, because of the multiplicity of chiral bisphosphines which are suitable for constructing support-bonded catalysts, a large number of different heterogeneous bisphosphine components can be provided in order, in combination with the amine components of the catalyst system, to achieve the optimum processing method for the substrate in question.

Catalysts which contain support-bonded bisphosphine ligands and which are suitable as precursors for the novel catalysts used according to the invention are known or can be obtained analogously to the preparation of ones which are known (see e.g. J. Org. Chem. 63, 3137 (1998), GB-A 96-19684, EP-A 496 699, EP-A 496 700, EP-A 728 768, J. Mol. Catal. A 107 (1-3), 273 (1996) and 13th International Conference on Org. Synth., Warsaw, July 1-5, 2000, Book of Abstracts, PB-4, p. 227).

A process for the preparation of non-chiral alcohols using such catalysts in the presence of amines and a base has not, however, hitherto been considered.

According to the invention, alcohols are obtained by reacting a carbonyl compound with hydrogen in an advantageous manner if the hydrogenation is carried out using a catalyst of the formula (I) in the presence of a base.

[support]-[optional modification]-[binding group]-

-[bisphosphine $>RuHal_2<$ diamine] (I),

where

Hal is chlorine or bromine.

It is also possible to carry out the hydrogenation using a support-bonded, insoluble catalyst of the formula (II) if both a base and also a diamine are present in the reaction mixture at the same time during the hydrogenation. In this case, a catalyst of the formula (I) is formed in situ.

[support]-[optional modification]-[binding group]-

-[bisphosphine $>Ru<^{Hal}_{Hal}$] (II),

where

Hal is chlorine or bromine.

Preference is, however, given according to the invention to using catalysts of the formula (I) which already contain support-bonded Ru(II) complexes which in each case contain both bisphosphine and also diamine ligands.

Suitable supports for the catalyst to be used according to the invention are inorganic materials, e.g. silica gels, and organic materials, e.g. crosslinked polymers.

Organic catalyst supports are, for example, crosslinked bead polymers which can be obtained by suspension polymerization with the addition of bifunctional monomers from styrene, acrylates or methacrylates or (meth)acrylamides.

In order to permit a binding of the bisphosphine ligands, these supports must contain reactive groups. Suitable for this purpose are, for example, primary and secondary amino groups, hydroxyl, carboxyl and isocyanate groups, and groups which contain reactive halogen, such as benzylic chlorine or bromo(ar)alkyl.

Such groups can be introduced as early as during the preparation of the bead polymer using functional comonomers such as acrylic acid, methacrylic acid, 2-hydroxyethyl acrylate, 2-methyl-2-isocyanato-propyl acrylate or by subsequent modification of the support, e.g. by chloromethylation of the crosslinked polystyrene bead polymer, which may optionally be followed by a further functionalization, such as, for example, saponification and polyether grafting. The preparation of such polymers with reactive groups is known.

It has proven advantageous to arrange the modification of the support such that a greater distance is maintained between support and bisphosphine, a spacer being advantageous which consists of an alkylene or aralkylene or an alkyleneoxy chain optionally with incorporated ester, ether, amide, urethane or urea groups and includes at least 12 atoms between support and bisphosphine.

Silica gels and similar anorganic support materials can be modified, for example, by reaction with 3-aminopropyl-trioxysilane in order to get reactive amino groups bounded to the support material

For the preparation of the catalysts used according to the invention, chelate-forming bisphosphines are used which contain functional groups which can generate a covalent bond with reactive groups on a suitable or suitably modified, insoluble support.

Examples of functional groups of the bisphosphine derivatives used for linking with the reactive groups of the above-described, optionally correspondingly modified supports which may be mentioned are: aromatically or (ar)aliphatically bonded primary or secondary amino

groups, aromatically or (ar)aliphatically bonded hydroxyl groups, carboxyl and isocyanate groups, and aromatically bonded chloromethyl and chlorosulphonyl groups.

The linking can be carried out either with correspondingly functionalized bisphosphines and also with the analogous bisphosphine oxides. If chlorosulphonyl or chloromethyl groups are used, the procedure on the bisphosphine oxide stage is obligatory in order to avoid secondary reactions.

In the case of linking with the polymeric support on the phosphine oxide stage, it is necessary to subsequently reduce the support-bonded bisphosphine oxide in a manner known per se using silanes in the presence of tertiary amines to give the polymer-bonded bisphosphine.

Correspondingly, for example, bindable functional-group-containing derivatives of 1,2-bis(diphenylphosphino-)ethane, 1,2- and 1,3-bis(diphenylphosphino-)propane, (phenylene-1,2-diyl)bis(diphenylphosphine), pyrrolidin-3,4-diyl)-bis(diphenylphosphine) (unmodified) are used, and, in particular for the preparation of enantioselectively effective catalysts, derivatives with bindable functional groups of the chirally uniform chelating bisphosphines Dipamp, Prophos, Norphos, Chiraphos, Deguphos (unmodified), Diop, ModDiop, Bppm, ModBppm, Duphos and BppfOH (unmodified) are used (for the abbreviations see Handbook of Enantioselective Catalysis, Ed. H. Brunner, W. Zettlmeier, VCH Verlag Weinheim, 1993).

Particular preference is given to using derivatives of atropisomeric bisphosphines which contain groups suitable for the linking, in particular those in chirally uniform form, as building blocks for the catalysts according to the invention. Examples which may be listed here are enantiomerically pure derivatives, containing bindable functional groups, of 2,2'-bis(diarylphosphino)-1,1'-binaphthylene, such as 5,5'-diamino-2,2'-bis(diphenylphosphino)-1,1-binaphthyl, 7,7'-dihydroxy-2,2'-bis(di-(m-xylyl)phosphino)-1,1'-binaphthyl, 4-(2,2'-bis(diphenylphosphino)-1,1'-binaphth-6-yl)butanoic acid, 4-(2,2'-bis(diphenylphosphino)-1,1'-binaphth-6-yl)butanol, or derivatives, containing groups able to link with suitable supports, of at least in 6,6'-position-substituted (biphenyl-2,2'-diyl)bis(diarylphosphines), (biphenyl-2,2'-diyl)bis(dicycloalkylphosphines) or (biphenyl-2,2'-diyl)bis(dihetarylphosphines), such as, for example, (6,6'-dihydroxybiphenyl-2,2'-diyl)bis(diphenylphosphine), (6-hydroxy-6'-methoxybiphenyl-2,2'-diyl)bis(di-(m-xylyl)phosphine, (6,6'-dihydroxy-biphenyl-2,2'-

diyl)bis(dicyclohexylphosphine) and (6,6'-dihydroxybiphenyl-2,2'-diyl)bis(di-thien-2-ylphosphine).

Optionally modified support material and modified phosphine are then combined such that both components can form a chemical bond with one another. One component may contain, for example, COOH groups and the other component may contain NH_2 groups, which can react with one another to form -CO-NH bonds. Depending on the combination of reactive groups chosen, various types of bonds can be realised, e.g. as well as -CO-NH-, also -CO-NR-, CO-O-, -O-, -OCONH-, -NH-CO-NH, -O-CO-NR- and -O-CO-O-. The methods of coupling correspondingly reactive substances to supports are known.

The bisphosphines are then bonded to a support.

In order to obtain heterogeneous Ru(II)-phosphine complex catalysts of the formula (II) to be used according to the invention, the phosphines bonded to a support can be reacted with suitable Ru(II) complexes. The Ru(II) complexes used for this purpose are, for example, the complexes of the formula

$[Ru(aren)X_2]_2$,

in which

X is Cl or Br,

such as, for example, (p-cymene)-ruthenium(II) chloride, dimer, (see J. Org. Chem., 59, 3064, 1994). In particular, bis-(2-methallyl-cyclooct-1,5-diene-Ru(II) complex is suitable for the preparation of catalysts of the formula (II) (see Tetrahedron: Asymmetry, Vol. 2, No. 7, p. 565, 1991).

To prepare catalysts of the formula (I), for example the heterogeneous precursor of the formula (II) is suspended in solutions of the diamine. The solvents used for this purpose are, for example, dichloromethane, acetonitrile or DMF. 1 to 10 equivalents of the diamine based on Ru are used in dilute solution, and the reaction is for example carried out under a

protective gas, preferably argon, at temperatures of from 20° to 100°C over the course of from about 3 to 48 hours. The catalyst of the formula (I) filtered off under a protective gas and washed out is dried under reduced pressure and is storage-stable.

Suitable carbonyl compounds for use for the process according to the invention are, for example, those of the formula (V)

$$R^1\text{-}CO\text{-}R^2 \qquad (V),$$

in which

R^1 and R^2 may be identical or different and are in each case hydrogen, straight-chain or branched C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl or C_2-C_{12}-alkinyl, are C_2-C_8-cycloalkyl, C_6-C_{12}-aryl or C_4-C_{11}-heteroaryl having in each case 1 to 3 ring heteroatoms from the groups N, O or S.

Alkyl, alkenyl, alkinyl and cycloalkyl radicals can optionally be substituted by halogen, hydroxyl, di-C_1-C_{12}-alkylamino, C_6-C_{10}-aryl-C_1-C_{12}-alkylamino, di-C_6-C_{10}-arylamino, C_1-C_{12}-alkoxy, C_1-C_{12}-alkoxycarbonyl, amide and/or urethane groups, where, for example, up to 3 identical or different substituents may be present.

Aryl and heteroaryl radicals can optionally be substituted by C_1-C_{12}-alkyl, di-C_1-C_{12}-alkylamino-C_1-C_{12}-alkyl, halogeno-C_1-C_{12}-alkyl, hydroxy-C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkinyl, halogeno, C_1-C_{12}-alkoxy, halogeno-C_1-C_{12}-alkoxy, C_6-C_{10}-aralkoxy, hydroxyl, carboxyl, C_1-C_{12}-alkoxycarbonyl, amide and/or urethane groups, where, for example, up to 3 identical or different substituents may be present.

R^1 and R^2 can together with the CO group in between also form a cyclo-C_4-C_{12}-alkyl ketone, where the cycloalkyl moiety may be substituted as given above for R^1 = alkyl, and may also be unsaturated.

The alkyl groups, including those in combined radicals, are preferably C_1-C_6-alkyl groups. The alkenyl and alkinyl groups, including those in combined radicals, are preferably C_2-C_4-alkenyl or C_2-C_4-alkinyl groups.

The cycloalkyl groups, including those in combined radicals, are preferably C_4-C_7-cycloalkyl groups.

The aryl groups, including those in combined radicals, are preferably C_6-C_{10}-aryl groups, and the heteroaryl groups are preferably those which contain 5 to 9 ring carbon atoms.

The alkoxy groups in combined radicals are preferably C_1-C_6-alkoxy groups.

Halogen in combined radicals is preferably fluorine or chlorine.

Particularly preferred alkyl groups are:
methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, pentyl, hexyl, heptyl, chloromethyl, 2-chloroethyl, 2-hydroxyethyl, 2-dibenzylaminoethyl, 2-(N-benzyl-N-methylamino)-ethyl, 2-ethoxyethyl, methoxycarbonylmethyl, 2-(N-methyl-N-methoxycarbonylamino)-ethyl, vinyl, methallyl, propinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-methyl-cyclohexyl, benzyl, pyridyl-2-methyl and (5-trifluoromethyl-pyridyl-2)-methyl.

Particularly preferred aryl groups are:
phenyl, 2-methylphenyl, 2-ethylphenyl, 2-isopropylphenyl, 2-tert-butylphenyl, 3-pentylphenyl, 4-isobutylphenyl, 2,3-dimethylphenyl, 2,4,6-trimethylphenyl, 2-(2-dimethylaminoethyl)-phenyl, 2-trifluoromethylphenyl, 4-(2-hydroxyethyl)-phenyl, 3-vinylphenyl, 4-(propinyl-1)-phenyl, 4-benzylphenyl, 2-chlorophenyl, 3-fluorophenyl, 2-methoxyphenyl, 3,4-dimethoxyphenyl, 4-benzyloxyphenyl, 1-naphthyl, 2-naphthyl and 2-indenyl.

Particularly preferred hetaryl groups are:
pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thienyl, furyl, oxazolyl and indolyl, suitable substituents being those which have been given above for particularly preferred aryl groups.

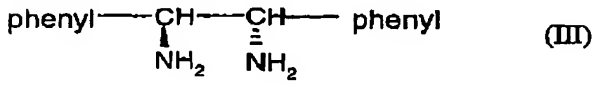
Particularly preferred cyclo-C_4-C_{12}-alkyl ketones are:
cyclobutanone, cyclopentanone, cyclohexanone, 4-methyl-cyclohexanone, 2-methyl-cyclohexanone, 2-tert-butyl-cyclohexanone, 4-tert-butyl-cyclohexanone, cyclohexanone and 2,4,4-trimethyl-2-cyclohexanone.

Bases which may be used in the process according to the invention are, for example, hydroxides or alkoxides of alkali metals or quaternary ammonium hydroxides. These are, in particular, lithium, sodium or potassium hydroxides, lithium, sodium or potassium C_1-C_4-alkyl alkoxides or tetra-C_1-C_4-alkylammonium hydroxides. Particular preference is given to potassium hydroxide, lithium hydroxide, potassium methoxide, sodium methoxide, sodium isopropoxide, potassium tert-butoxide, tetramethylammonium hydroxide and tetrabutylamonium hydroxide.

For the preparation of the catalyst of the formula (I), suitable diamines are those which can form a chelate complex with Ru(II). For example, mention may be made of: 1,2-diamino-ethane, 1,2- and 1,3-diaminopropane, 1,2-diaminobutane, 2,3-diaminobutane, 2,3-diamin-opentane, 1,2-diamino-1,2-diphenylethane, 1,2-diaminocyclopentane, 1,2-diamino-cyclohexane, 1,2-diamino-methyl-cyclohexane, 1-amino-2-N-methylamino-ethane and 1-amino-1-methyl-2-N-methylaminocyclohexane.

Preferred optically active amines for the preparation of the support-bonded catalysts of the formula (I) are chirally uniform diamines, in particular those derived from 1,2-diamino-ethane and from 1,2-diaminocyclohexane and can contain, as substituents, optionally C_1-C_8-alkyl, C_4-C_8-cycloalkyl, C_6-C_{10}-aryl-C_1-C_8-alkyl, C_2-C_8-alkenyl and/or C_6-C_{10}-aryl groups optionally substituted by C_1-C_8-alkyl and/or C_1-C_8-alkoxy.

For the preparation of the novel catalysts of the formula (I), particular preference is given to the diamines of the formulae (III) and (IVa-c):



(III)

(IVa-IVc)

(IVa): $R = CH_3$

(IVb): $R = CH(CH_3)_2$

(IVc): $R = CH_2\text{-}CH(CH_3)_2$

For the preparation according to the invention of optically active alcohols, these optically active amines can be used either as (S,S)-, (R,R)-, (R)- or (S)-stereoisomers.

These stereoisomers can be prepared in a known manner or analogously thereto (see e.g. Tetrahedron, Lett. 34 (12), 1905 (1993). Which optically active amine in which form in combination with a certain catalyst to be used according to the invention in the preparation according to the invention of a certain optically active alcohol affords optimum results can be ascertained, if desired, by routine experimental theories in accordance with the "in situ" variant of the process.

When the process according to the invention is carried out in accordance with the "in situ variant", if the procedure is discontinuous, i.e. in a stirred autoclave, the amount of a catalyst of the formula (II), calculated as moles of Ru(II), is, per mole of carbonyl compound, in the range from 1:100 to 1:100 000, and this amount is preferably 1:200 to 1:10 000.

The diamine can, based on heterogeneous Ru(II)-phosphine complex catalyst(s), (calculated as moles of Ru(II)), be used, for example, in amounts of from 1:0.5 to 1:4. This amount is preferably 1:1 to 1:2.5 per mole of Ru(II). The base can, based on the heterogeneous Ru(II)-phosphine complex catalyst (calculated as moles of Ru(II)), be used, for example, in amounts of from 0.5 to 1 000 equivalents. This amount is preferably 2 to 40 equivalents of base per mole of Ru(II).

If the process according to the invention is carried out using a separately isolated prepared catalyst of the formula (I), the amount of the catalyst (calculated as equivalents of Ru(II) per

mole of carbonyl compound used) may be 1:100 to 1:500 000. This amount is preferably 1:1 000 to 1:200 000.

In the case of the use of catalysts of the formula (I), an addition of diamine to the reaction mixture or to the solution of the substrate is not necessary, but may be advantageous to increase the service life of the heterogeneous catalyst. The amount of such an addition of diamine is in the range from 0.01 to 1.0 equivalents, based on moles of Ru(II) complex used.

For the amounts of base used, the ratios are the same as those which have been given above for the in situ variant.

It is advantageous to carry out the process according to the invention in the presence of solvents. Suitable solvents are those which do not react in an undesired manner with the materials used and have sufficient solubilizing power for the carbonyl compound used and the amine used. Examples are aliphatic hydrocarbons such as hexane and isooctane, aromatic hydrocarbons such as toluene and the xylenes, halogen-containing hydrocarbons such as methylene chloride, linear and cyclic aliphatic ethers such as tert-butyl methyl ether and tetrahydrofuran, C_1-C_8-alkyl and C_7-C_{10}-aralkyl alcohols such as methanol, ethanol, n-propanol, isopropanol and benzyl alcohol and dipolar-aprotic solvents such as acetonitrile, dimethylformamide and N-methylpyrrolidone.

Preferred solvents are C_1-C_4-alkyl alcohols, in particular isopropanol. It is also possible to use solvent mixtures.

It is possible to work without the addition of solvents or with solvent additions up to below a substrate concentration of 1% by weight or less. Solvent is preferably used in an amount such that a substrate concentration in the range from 10 to 50% by weight results.

The hydrogen pressure to be applied during the process according to the invention can, for example, be between 1 and 150 bar. It is preferably in the range from 3 to 120 bar, in particular between 5 and 100 bar.

The reaction temperature during the process according to the invention can, for example, be in the range from -20 to +120°C. It is preferably in a range from +15 to +100°C, in particular from +25 to +100°C.

The reaction time is dependent on the embodiment of the process and the reaction conditions. It is generally in a range of from, for example, 5 minutes to 12 hours.

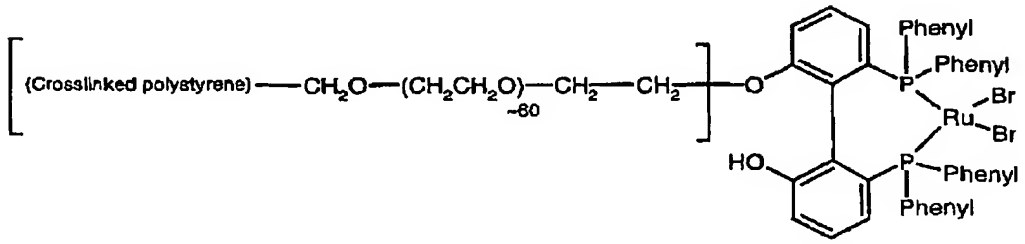
In the process according to the invention, the work-up of the reaction mixture is simple since the catalyst can be removed, for example, by filtration and the bases and amines present in the reaction mixture can be removed with the help of an ion exchanger. The isolated catalyst can be reused. The prepared, optionally optically active alcohols are not contaminated with catalysts or constituents thereof following work-up of the reaction mixture. The process according to the invention can also be carried out continuously without problems.

Surprisingly, the process according to the invention shows selectivities and activities that are at least comparable to homogeneous catalysts.

Examples

Example 1

A solution of 12 g of acetophenone in 100 ml of isopropanol with the addition of 500 mg of a support-bonded ruthenium complex of the formula (IIa)



(IIa)

[S-Atropisomer (content of Ru: 0.21 mmol/g)]

39 mg of (S)-1,1-di-(p-anisyl)-3-methyl-1,2-diamino-butane and 420 μl of a 0.5 molar solution of potassium hydroxide in isopropanol was degassed in a 250 ml stirred autoclave a number of times under freeze-drying conditions ("freeze-thaw cycles") and the gas phase was replaced by hydrogen. Hydrogen was then injected to a pressure of 50 bar at 40°C for 6 hours. The mixture is then filtered under a protective gas, and the reaction solution which remains was treated with an acidic ion exchanger resin, the diamine and potassium ions being bonded. After filtration, the laden exchanger resin was washed a number of times with isopropanol and the product solution, together with the wash phases, were distilled. 11.6 g of more than 99% pure 1-phenyl-ethanol with a content of 90% of R-enantiomer were obtained (CSP-HPLC analysis).

The recovered, support-bonded ruthenium complex and the diamine recovered and separated off by means of ion exchange were used in a further preparation process corresponding to Example 1 in place of fresh catalyst and fresh diamine. Virtually identical results were obtained.

Example 2

Preparation of the Ru complex used in Example 1

a) 0.5 g of (S)-6,6'-dihydroxydiphenyl-2,2'-diyl-bis-(diphenylphosphine), prepared in accordance with WO 93/15090, Example 1, were dissolved under argon in 50 ml of anhydrous and degassed tetrahydrofuran, and a suspension of 0.216 g of sodium hydride in 10 ml of dimethylformamide was added. The mixture was stirred for 60 minutes at room temperature. 4 g of TentaGel® S-bromide[1] were then added and the mixture was stirred for a further 48 hours at room temperature. The solid present was then filtered off, stirred with saturated aqueous ammonium chloride solution and then with 3 × 50 ml of anhydrous methanol and filtered. After the last filtration, the resulting product was dried under reduced pressure.

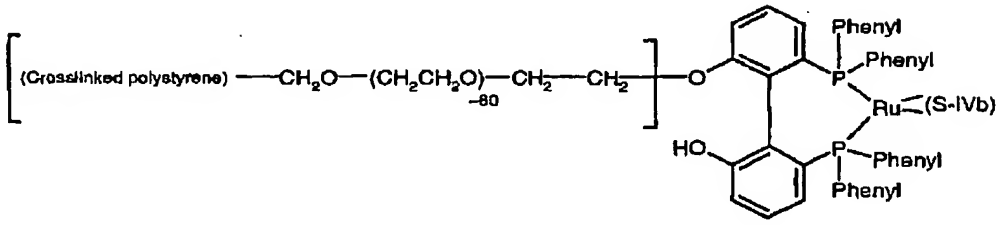
b) 800 mg of the modified support resin obtained according to a) and 53 mg of bis-(2-methallyl)-cycloocta-1,5-diene-Ru(II) complex were suspended under argon in 20 ml of anhydrous and degassed acetone and dissolved with stirring. 1.38 ml of 0.29 molar hydrogen bromide solution were then added. The mixture was stirred for 2 hours at room temperature, then filtered under argon. The solid obtained was washed under argon with acetone, then with isopropanol, until the filtrate was free from ruthenium.

After drying under reduced pressure, a ruthenium analysis revealed a loading of 0.21 mmol/g.

[1] TentaGel reactive resins (products from Rapp Polymere GmbH, Tübingen, Germany), are copolymers obtained by stepwise grafting of a crosslinked polystyrene matrix with polyethylene glycol and ethylene oxide according to EP 187 391. They contain freely movable end groups, e.g. in the case of TentaGel S-Br, the group CH_2-CH_2-Br.

Example 3

A solution of 12 g of acetophenone in 100 ml of isopropanol with the addition of 40 mg of a support-bonded ruthenium complex of the formula (Ia)



(Ia)

[S-Atropisomer (content of Ru: 0.20 mmol/g)]

and of 420 μl of a 0.5 molar solution of potassium hydride in isopropanol was degassed in a 250 ml stirred autoclave a number of times under freeze-drying conditions ("freeze-thaw cycles"), and the gas phase was replaced by hydrogen. Hydrogenation was then carried out with stirring at 40°C at a hydrogen pressure of 40 bar for 2 hours. Following filtration and washing out of the catalyst which remains as filter residue using 10 ml of isopropanol, the filtrate, combined with the wash solution, was distilled under reduced pressure, giving 11.7 g of pure 1-phenyl-ethanol with a content 90% of R-enantiomer (CSP-HPLC analysis).

Example 4

Preparation of the catalyst of the formula (Ia) used in Example 3

1 g of the catalyst of the formula (IIa) prepared as in Example 2 was added, under argon, to a degassed solution of 120 mg of (S)-1, 1-di-(p-anisyl)-3-methyl-1,2-diamino-butane in 20 ml of dichlormethane, and the mixture was kept at 25°C with stirring for 12 hours. After filtration under a protective gas, the resulting catalyst of the formula (Ia) was washed with 20 ml of dichloromethane and then dried under reduced pressure.

Patent claims

1. Process for the preparation of non-chiral or optically active alcohols in which a carbonyl compound is reacted with hydrogen in the presence of a catalyst, a base and optionally a diamine, characterized in that the catalyst used is an Ru(II) complex which contains both a support-bonded bisphosphine ligand and also a diamine ligand.

2. Process according to Claim 1, characterized in that the catalyst is formed in situ from a support-bonded precursor and a diamine.

3. Process according to Claim 1, characterized in that a catalyst is used which contains both a chirally uniform, support-bonded bisphosphine ligand and also a chirally uniform diamine ligand.

4. Process according to Claim 3, characterized in that an atropisomeric bisphosphine ligand is present in the catalyst.

5. Ru(II) complex catalyst, characterized in that the Ru complex contains a support-bonded bisphosphine ligand and a diamine ligand.

Abstract

Non-chiral and, in particular, optically active alcohols are prepared from a carbonyl compound with hydrogen in the presence of a catalyst, a base and optionally a diamine in an advantageous manner if a catalyst is used which contains both a support-bonded Ru(II) complex bisphosphine ligand and also a diamine ligand.